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Woods Hole Oceanographic Institution
Grant and Contract Services
183 Oyster Pond Rd.
Fenno House, MS #39
Woods Hole, MA 02543-1531

8. PERFORMING ORGANIZATION REPORT NUMBER

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14. ABSTRACT

The objective with this study is to determine if there is an allometric relationship between body mass and decompression sickness (DCS) risk over a large range of terrestrial mammals. We have modified a previously published probabilistic model to assess DCS risk for different species. The results will help determine if studies performed in different species and body sizes can be compared or if there are differences in risk not attributable to body size.

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a. REPORT	b. ABSTRACT	c. THIS PAGE		6	Andreas Fahlman
					19b. TELEPHONE NUMBER (include area code) 361-825-3489

Allometric Scaling of Decompression Sickness Risk in Terrestrial Mammals

Andreas Fahlman, Peter L. Tyack
Woods Hole Oceanographic Institution
266 Woods Hole Road, MS #50
Woods Hole MA 02543
email: ptyack@whoi.edu, afahlman@whoi.edu

Richard Mahon
Department of Undersea Medicine
Naval Medical Research Center
511A Robert Grant Ave, Silver Spring MD

Grant Number: N00014-10-1-0159/N00014-09-WR-20240

LONG-TERM GOALS

The objective with this study is to determine if there is an allometric relationship between body mass and decompression sickness (DCS) risk over a large range of terrestrial mammals. We have modified a previously published probabilistic model to assess DCS risk for different species. The results will help determine if studies performed in different species and body sizes can be compared or if there are differences in risk not attributable to body size.

OBJECTIVES

Background

Using animals in DCS research is of great importance as is it allows researchers to investigate the basic mechanisms of DCS and screen possible candidate drugs that might prevent or help treat or ameliorate DCS symptoms. The binary nature of DCS research with outcome being either yes or no requires a large number of DCS cases. To increase the power of such studies, they are usually limited to a single species within a certain weight limit, dive profile and gas mixture. Despite data from a variety of terrestrial mammal species in DCS research, it is still unknown if differences in susceptibility are caused merely by variation in M_b [1-3] or if additional factors play a role. Therefore, it is it is difficult to compare results from different laboratories that use different animal models.

Possible physiological variables that may affect DCS risk include body temperature (), body weight, exercise, gender, adiposity, age, serum cholesterol, sensitivity to complement activation, Doppler bubble grades and patent foramen ovale [4-8]. However, where some studies have found a correlation, others refute those results [9, 10]. The only physiological variable that has been undisputedly correlated with DCS risk in rats is body mass [11].

Tissue inert gas tension (P_{tis}) is predicted by:

$$\frac{dP_{tis}}{dt} = \frac{P_{blood}}{\tau} - \frac{P_{tis}}{\tau} \qquad \text{Eq. 1}$$

where P_{tis} is the tissue tension of the inert gas (ATA), P_{blood} is the arterial blood tension of the inert gas (ATA) , τ is the tissue time constant (min), and t is time (min). τ determines the flux of gases in and out of the tissues. The whole animal τ is the mean τ of all the different tissue compartments and a physiologically relevant parameter, related to the size of the animal (V) the solubility of the gas in the blood and tissue (λ) and the cardiac output (Q) as:

$$\tau = \frac{V}{\dot{Q}} \cdot \lambda$$ Eq. 2

As the mass-specific cardiac output (sQ) is allometrically related to M_b [12] DCS should follow a similar relationship if there are no differences in susceptibility between species.

We therefore aimed to compare DCS susceptibility of those species most commonly used in DCS research in an attempt to determine if differences in susceptibility among species can be explained by differences in M_b. If so, it will be easy to compare findings from different laboratories. If DCS risk cannot be scaled allometrically, we need to refine our understanding of the physiological differences among species that result in variation in DCS susceptibility. If such differences exist, future studies are required to determine the relative importance of species vs. allometric relationships. It is vital to account for any differences if the results are to be scaled to humans. This study therefore aimed at investigating if M_b can be used to scale DCS risk between species.

We used historical data from different terrestrial species and determine if DCS risk can be explained by M_b, once saturation depth and ascent rate are accounted for by accumulating risk during the ascent. We used the probabilistic model pioneered by Weathersby et al. [13] and adjusted for M_b between species to account for accumulation of risk during the ascent. While previous descriptive dose response models have suggested that DCS risk can be scaled between species [1-3] the model used in this study offers a predictive advantage over the.

Our objective was to test the following hypotheses 1) Determine if there is a simple relationship between DCS risk and M_b within and among different terrestrial mammalian species or if susceptibility differs. 2) Using animal data to predict DCS risk in humans after air saturation dives.

APPROACH

1. Determine if there is a simple relationship between DCS risk and M_b within and among different terrestrial mammalian species or if susceptibility differs.
2. Using animal data to predict DCS risk in humans.
    a. If M_b alone can be used to predict, we will apply data from the species used in animal research to predict DCS risk in humans.
    b. If susceptibility differs, we will determine scaling factors to be used to compare risk among species. This scaling factor will determine if it is possible to predict DCS risk in humans from animal data.

WORK COMPLETED

Air saturation data were collected from the literature and from on-going studies. A total of 2304 dive profiles were summarized for the mouse (592), hamster (732), rat (625), dog (174), and pig (166, Table 1). Due to a reduction in the funding level, we were not able to obtain historical dive data from the rat (from Dr. Richard Lillo) or the sheep (from Dr. Marlowe Eldridge). Instead, rat data were taken from various published peer-reviewed papers (Table 1). Due to the uncertainty in the previously published sheep data [14] we excluded sheep from the analysis.

Species	Number of animals	Number of dive profiles	Number of DCS cases	O2 partial pressure (ATA)	Average body mass (kg)	Pressure range (ATA)	Decompression rate (ATm min^{-1})	Time at depth (min)	Reference

Mouse	240 (120)	6	145	0.5-1.0	0.02	14.2-15.2	142-164	30	[15]
Mouse	64 (64)	8	26	0.3	0.02	14.8	1.4-104	16	[2]
Mouse	288 (40)	2	114	0.5	0.02	13.8-14.2	43	15	[16]
Hamster	732 (200)	5	403	1.2-2.2	0.1	5.7-10.5	38-185	31	[17]
Rat	195 (195)	13	136	1.0	0.26	6.26-7.26	2.2-89	60	[18]
Rat	80 (45)	3	56	1.0	0.25-0.27	6.3	76	60-120	[19]
Rat	350 (120)	10 (6)	209	1.1-1.6	0.23-0.25	6.3-7.7	75-96	120	[20]
Dog	30 (174)	8	27	0.5-0.8	19.2±3.8	2.5-3.9	1.2-1.3	300	[21]
Pig	125	14	70	0.5-1.0	21.0±0.0	2.5-5.6	0.9	1440	[22]
Pig	41	4	15	0.4-0.6	69.2±4.0	1.9-2.8	0.9	1440	unpublished
Total	**2160 (1124)**	**74**	**1201**	**0.3-2.2**	**69.2-0.02**	**1.9-15.2**	**0.9-156**	**15-1440**	

[Table 1. Dive data sets used for modeling. Data included number of animals (number within parenthesis for dogs is total number of dive profiles as some animals did repeated exposures with at least a week in between dives), number of dive profiles, the O2 partial pressure at depth, the average reported body mass (kg), the pressure range for the different dive profiles, the decompression rate (ATM min-1) and the reference where the data was published. Values for number of animals and dive profiles in parenthesis is for reduced data set. For the dog, 30 animals were used and these were dived repeatedly at higher pressures until exhibiting DCS symptoms after which they were removed from the study. Value for the dig in parenthesis is the total number of dives in that study.]

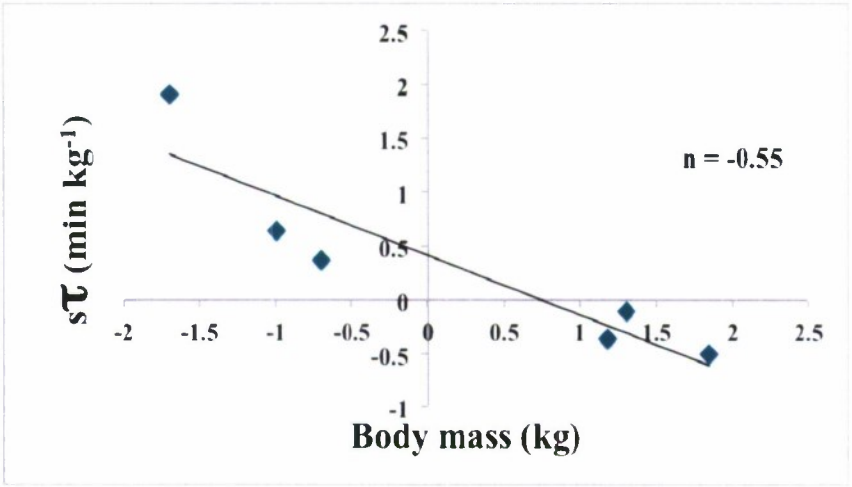
The additional work to gather dive data from the literature took approximately 6 months, which reduced the time to complete aim 2. Thus, we are still working on finishing aim 2 and we expect this to be completed in 2012.

A previously published [23] probabilistic model was used to estimate the inert gas tissue time constant (τ) following air saturation dives. The time constant determines the time to equilibrium, is physiologically relevant and related to the solubility of the gas and the blood flow rate. The allometric mass-exponent (n), that relates the mass-specific blood flow rate with M_b, ranges between 0.25 to 0.33 in mammals. It was hypothesized that DCS risk would similarly scale with size. To test this hypothesis, τ was adjusted by $\tau \bullet M_b^{-n}$, where n' is the mass-exponent for DCS. If DCS risk is directly related to the cardiac output, n will be similar to the mass-exponent for blood flow.

RESULTS

Aim 1) The mass-specific τ ($s\tau$, min $\bullet$ kg^{-1}) was determined for each species and plotted against M_b and the resulting n was -0.55 (Fig. 1). When the data were pooled, the best model included n' (-0.91),

two τ's (0.7 and 123 min), a threshold parameter (Thr, 1.45 ATA), and two dummy variables that adjusted risk for the dog (0.05) and pig (0.24).



[Figure 1. Scatter plot showing the mass-specific time constant (st) for each species against body mass (kg).]

The binary nature of DCS research with outcome being either yes or no requires a large number of DCS cases. To increase the power of the current study, we limited the data to air saturation dives where the M_b had been reported. In addition, a model used to predict DCS should be calibrated with high quality data, selected with the application in mind, and a perfect model will fit all data very well. The process of calibrating an imperfect model to a large dataset spreads the model "error" over all observations, without any regard for which aspects the analyst personally considers most important. Therefore, the set should not be dominated by any one data feature, to the relative exclusion of another that may be as important. However, to make useful predictions the calibration data set need to contain sufficient number of DCS cases to allow adequate parameter fitting. Consequently, carefully selecting the data set to be used is a time-consuming but vitally important process for useful model estimates. For this reason, we hypothesized that the dummy variables needed for the dog and pig were required because the number of observations were much less than for the other species. We therefore reduced the number of observations for the rat, mouse and hamster so that number of observations within each species would be more comparable (mouse (224), hamster (200), rat (360), dog (174), and pig 166, Table 1). The adjusted data included all dive profiles as the full data set, and the risk of DCS was the same for each dive profile. The best model for the reduced data set included n' (-0.87), two τ's (0.27 and 227 min), a threshold parameter (Thr, 1.07 ATA). However, no dummy variables that adjusted risk, threshold, or the mass-exponent between species were warranted.

Aim 2) We have gathered human air saturation data from 59 different dive profiles (ASATARE, ASATNSM, ASATNMR, NMR9209, EDUAS45, ASATDC, ASATFR85) with a total of 227 exposures [24]. The data set includes 25 certain DCS cases and 11 marginal cases [25]. We are using these data to determine if the parameter from the animal model can be used to predict DCS risk from each of these dive profiles.

IMPACT/APPLICATIONS

Using animals in DCS research provides the ability to study high risk dive profiles which in itself is important. Such research allows us compare pharmaceutical compounds that may prevent or help treat DCS symptoms. However, if these are to be useful for humans, we need to understand how to compare results among different species used for research and how this translates to humans. Without this understanding, results from different studies and species cannot be compared, wasting research funds and time without any meaningful results.

Previous modeling studies and experimental work have shown the benefit of using animal data to improve DCS predictions for humans. The important question addressed in this study is whether a single scaling factor can be used for different species or whether there are real species differences in susceptibility. If so, this has to be adjusted for when results are compared among species and when scaled to humans. This is important, not only for its utility in predicting human risk, but will ultimately helping to define the physiological basis of scaling DCS across species. Such knowledge conceivably would not only allow normalization of DCS risk across species by scaling variables such as blood flow or volume of evolved gas, but perhaps more importantly, help us better understand the pathophysiology of DCS. Thus, the proposed work investigated the fundamental basis of DCS and has enhanced our understanding of how better to use historical and future animal data to improve diving mission safety. In addition, this approach may allow testing of high-risk dives, reducing the need for costly, time consuming manned trails, and improve prediction of human dives.

The results suggest that the probability of DCS for air saturation dives can be scaled between species ranging in M_b over 3 orders of magnitude. However, the magnitude of n' and the dummy parameters for dog and pig, suggest that DCS susceptibility may vary between species. Thus, interpretation between species, even of similar size such as that for 70 kg pig to man, should be made with caution. Further studies are necessary to determine if the differences in susceptibility are due to experimental conditions such as greatly differing dive profiles in small vs. large mammals (explosive vs. slower decompression, respectively), continuous chamber exercise (rats) vs. brief exercise (pigs), or biochemical or physiological species differences.

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